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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/CA98/00487 <b>(22) International Filing Date:</b> 22 May 1998 (22.05.98)  <b>(30) Priority Data:</b> 08/861,747 22 May 1997 (22.05.97) US  <b>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application</b> US 08/861,747 (CIP) Filed on 22 May 1997 (22.05.97)  <b>(71) Applicant (for all designated States except US):</b> ALLELIX BIOPHARMACEUTICALS, INC. [CA/CA]; 6850 Goreway Drive, Mississauga, Ontario L4V 1V7 (CA).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> MUNROE, Donald, G. [CA/CA]; 27 Wakefield Lane, Waterdown, Ontario L0R 2H3 (CA). VYAS, Tejal, B. [CA/CA]; 275 Riel Drive, Mississauga, Ontario L5B 3K1 (CA).	<b>(74) Agents:</b> CHARI, Santosh, K. et al.; Orange & Associates, Toronto Dominion Bank Tower, Toronto-Dominion Centre, Suite 3600, P.O. Box 190, Toronto, Ontario M5K 1H6 (CA).  <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>With amended claims.</i>	
<b>(54) Title:</b> A HUMAN EDG-6 RECEPTOR HOMOLOGUE  <b>(57) Abstract</b>  An isolated nucleic acid sequence coding for an amino acid sequence for a novel human EDG-6 receptor homologue is provided. Also provided are purified human EDG-6 receptor polypeptides derived from the nucleic acid and methods and transgenic animals therefor.		

## A HUMAN EDG-6 RECEPTOR HOMOLOGUE

### FIELD OF THE INVENTION

5           The present invention is in the field of molecular biology; more particularly, the present invention describes a nucleic acid sequence and an amino acid sequence for a novel human EDG-6 receptor homologue.

### BACKGROUND OF THE INVENTION

10           The family of edg (endothelial differentiation gene) receptors are commonly grouped with orphan receptors because their endogenous ligands are not known (for example see Hla, T. and Maciag, T. (1990) J. Biol. Chem. 265:9308-13; US patent 5,585,476). Recently, however, lysophosphatidic acid (LPA) has been demonstrated to be the endogenous  
15           ligand for the edg-2 receptor (Hecht et al. (1996) J. Cell. Biol. 135: 1071-1083; An et al. (1997) Biochem. Biophys. Res. Comm. 213: 619-622).

          The edg family of receptors are seven transmembrane G protein coupled receptors (T7Gs). T7Gs are so named because of their seven hydrophobic domains which span the plasma membrane and form a bundle of antiparallel  $\alpha$  helices. These transmembrane  
20           segments (TMS) are designated by roman numerals I-VII and account for structural and functional features of the receptor. In most cases, the bundle of helices forms a binding pocket; however, when the binding site must accommodate more bulky molecules, the extracellular N-terminal segment or one or more of the three extracellular loops participate in binding and in subsequent induction of conformational change in intracellular portions of the  
25           receptor. The activated receptor, in turn, interacts with an intracellular G-protein complex which mediates further intracellular signaling activities generally the production of second messengers such as cyclic AMP (cAMP), phospholipase C, inositol triphosphate or ion channel proteins.

          T7G receptors are expressed and activated during numerous developmental and  
30           disease processes. Identification of a novel T7G receptor provides the opportunity to diagnose or intervene in such processes, and the receptor can be used in screening assays to identify physiological or pharmaceutical molecules which trigger, prolong or inhibit its activity.

## SUMMARY OF THE INVENTION

The invention provides a unique nucleotide sequence which encodes a novel human  
5 EDG-6 receptor homologue (HEDG). Herein, the nucleotide sequence encoding HEDG is  
designated hedg. Thus, the invention provides an isolated nucleic acid molecule wherein the  
nucleic acid molecule encodes a polypeptide having an amino acid sequence as shown in  
SEQ. ID NO:2.

In another embodiment, the invention provides an isolated nucleic acid molecule  
10 having a nucleotide sequence as shown in SEQ. ID NO:1.

In yet another embodiment, the invention provides a nucleic acid molecule which is  
anti-sense to the molecules indicated above.

In a further embodiment, the invention provides for expression vectors, probes and  
DNA constructs based on the polynucleotides mentioned above.

15 In another embodiment, the invention provides for a purified polypeptide having the  
amino acid sequence as shown in SEQ. ID NO:2.

The invention also provides for antibodies specific to the above polypeptide.

In another embodiment, the invention provides for methods of purifying and assaying  
polypeptides as indicated above.

20 In a further embodiment, the invention provides for transgenic animals which include  
the nucleotide sequence of the invention.

## BRIEF DESCRIPTION OF THE DRAWINGS

25 Figures 1A and 1B shows the alignment of the nucleic acid sequence (coding region  
of SEQ. ID NO: 1) and amino acid sequence (SEQ. ID NO:2) for HEDG.

Figure 2 displays the nucleic acid sequence (SEQ. ID NO:3) of a cDNA encoding  
HEDG.

## 30 DETAILED DESCRIPTION OF THE INVENTION

As used herein and designated by the upper case abbreviation, HEDG, refers to an  
EDG-6 receptor homologue in either naturally occurring or synthetic form and active  
fragments thereof which have the amino acid sequence of SEQ. ID NO:2. In one

embodiment, the polypeptide HEDG is encoded by mRNAs transcribed from the cDNA, as designated by the lower case abbreviation, hedg, of SEQ. ID NO:1.

The novel human EDG-6 receptor homologue, HEDG, was cloned and isolated from a human kidney proximal tubule cDNA library. It shows 52.9% identity to human edg-2  
5 (WO 97/00952).

An "oligonucleotide" is a stretch of nucleotide residues which has a sufficient number of bases to be used as an oligomer, amplimer or probe in a polymerase chain reaction (PCR). Oligonucleotides are prepared from genomic or cDNA sequence and are used to amplify, reveal or confirm the presence of a similar DNA or RNA in a particular cell or  
10 tissue. Oligonucleotides or oligomers comprise portions of a DNA sequence having at least about 10 nucleotides and as many as about 35 nucleotides, preferably about 25 nucleotides.

"Probes" may be derived from naturally occurring or recombinant single - or double - stranded nucleic acids or be chemically synthesized. They are useful in detecting the presence of identical or similar sequences.

15 A "portion" or "fragment" of a polynucleotide or nucleic acid comprises all or any part of the nucleotide sequence having fewer nucleotides than about 6 kb, preferably fewer than about 1 kb which can be used as a probe. Such probes may be labeled with reporter molecules using nick translation, Klenow fill-in reaction, PCR or other methods well known in the art. After optimizing reaction conditions to eliminate false positives, nucleic acid  
20 probes may be used in Southern, Northern or in situ hybridizations to determine whether DNA or RNA encoding HEDG is present in a cell type, tissue, or organ.

"Reporter" molecules are those radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents which associate with, establish the presence of, and may allow quantification of a particular nucleotide or amino acid sequence.

25 "Recombinant nucleotide variants" encoding HEDG may be synthesized by making use of the "redundancy" in the genetic code. Various codon substitutions, such as the silent changes which produce specific restriction sites or codon usage-specific mutations, may be introduced to optimize cloning into a plasmid or viral vector or expression in a particular prokaryotic or eukaryotic host system, respectively.

30 "Chimeric" molecules may be constructed by introducing all or part of the nucleotide sequence of this invention into a vector containing additional nucleic acid sequence which might be expected to change any one (or more than one) of the following

## SEQUENCE LISTING

## (1) GENERAL INFORMATION:

- (i) APPLICANT: MUNROE, Donald G.  
VYAS, Tejal B.
- (ii) TITLE OF INVENTION: A HUMAN EDG-6 RECEPTOR HOMOLOG
- (iii) NUMBER OF SEQUENCES: 7
- (iv) CORRESPONDENCE ADDRESS:
  - (A) ADDRESSEE: Nikaido, Marmelstein, Murray & Oram LLP
  - (B) STREET: 655 15th St., NW, Suite 330 - G Street Lobby
  - (C) CITY: Washington
  - (D) STATE: DC
  - (E) COUNTRY: USA
  - (F) ZIP: 20005-5701
- (v) COMPUTER READABLE FORM:
  - (A) MEDIUM TYPE: Floppy disk
  - (B) COMPUTER: IBM PC compatible
  - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
  - (D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- (vi) CURRENT APPLICATION DATA:
  - (A) APPLICATION NUMBER: US 08/861,747
  - (B) FILING DATE: 22-MAY-1997
  - (C) CLASSIFICATION:
- (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Jahns, Kristina M.
  - (B) REGISTRATION NUMBER: 41,092
  - (C) REFERENCE/DOCKET NUMBER: P8074-7003
- (ix) TELECOMMUNICATION INFORMATION:
  - (A) TELEPHONE: (202) 638-5000
  - (B) TELEFAX: (202) 638-4810

## (2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1761 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: double
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

CGCTCCCGCC GCAGTCGCCG GGCCATGGGC CTCGAGCCCG CCCC GAACCC CCGCGAGCCC	60
GCCTTGCTCTG CGGCGTGACT GGAGGCCAG ATGGTCATCA TGGGCCAGTG CTACTACAAC	120
GAGACCATCG GTTCTTCTA TAACAACAGT GGCAAAGAGC TCAGCTCCCA CTGGCGGCC	180

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AAGGATGTGG TCGTGGTGGC ACTGGGGCTG ACCGTCAGCG TGCTGGTGCT GCTGACCAAT      240
CTGCTGGTCA TAGCAGCCAT CGCCTCCAAC CGCCGCTTCC ACCAGCCCAT CTACTACCTG      300
CTCGGCAATC TGGCCGCGGC TGACCTCTTC GCGGGCGTGG CCTACCTCTT CCTCATGTTC      360
CACACTGGTC CCCGCACAGC CCGACTTTCA CTTGAGGGCT GGTTCCTGCG GCAGGGCTTG      420
CTGGACACAA GCCTCACTGC GTCGGTGGCC ACACTGCTGG CCATCGCCGT GGAACGGCAC      480
CGCAGTGTGA TGGCCGTACA GTTGACAGC CGCCTGCCCC GTGGCCGCGT GGTTCATGCTC      540
ATTGTGGGCG TGTGGGTGGC TGCCCTGGGC CTGGGGCTGT TGCTGCCCCA CTCCTGGCAC      600
TGCTCTGTG CCCTGGACCG CTGCTCACGC ATGGCACCCC TGCTCAGCCG CTCCTATTG      660
GCCGTCTGGG CTCTGTGAG CCTGCTTGTG TTCCTGCTCA TGGTGGCTGT GTACACCCGC      720
ATTTTTTTAT ACGTGC GGCG GCGAGTGCAG CGCATGGCAG AGCATGTCAG CTGCCACCCC      780
CGCTACCGAG AGACCACGCT CAGCCTGGTC AAGACTGTTG TCATCATCCT GGGGGCGTTC      840
GTGGTCTGCT GGACACCAGG CCAGGTGGTA CTGCTCCTGG ATGGTTTAGG CTGTGAGTCC      900
TGCAATGTCC TGGCTGTAGA AAAGTACTTC CTA CTGTTGG CCGAGGCCAA CTCACTGGTC      960
AATGCTGCTG TGTACTCTTG CCGAGATGCT GAGATGCGCC GCACCTTCCG CCGCCTTCTC     1020
TGCTGCGCGT GCCTCCGCCA GCCCACC CGC GAGTCTGTCC ACTATACATC CTCTGCCCAG     1080
GGAGGTGCCA GCACTCGCAT CATGCTTCCC GAGAACGGCC ACCCACTGAT GGACTCCACC     1140
CTTTAGCTAC CTTGAATTTC AGCGGTACGC GGCAAGCAAC AAATCCACAG CCCCTGATGA     1200
CTTGTGGGTG CTCCTGGCTC AACCCAAACCA ACAGGACTGA CTGACCGGCA GGACAAGGTC     1260
TGGCATGGCA CAGCACCCT GGCAGGCCTC CCCAGGCACA CCACTCTGCC CAGGGAATGG     1320
GGGCTTTGGG TCATCTCCA CTGCTGGGG GAGTCAGATG GGGTGCAGGA ATCTGGCTCT     1380
TCAGCCATCC CAGGTTTAGG GGGTTTGTAA CAGACATTAT TCTGTTTTCA CTGCGTATCC     1440
TTGGTAAGCC CTGTGGACTG GTTCCTGCTG TGTGATGCTG AGGGTTTTAA GGTGGGGAGA     1500
GATAAGGGCT CTCTCGGGCC ATGCTACCCG GTATGACTGG GTAATGAGGA CAGACTGTGG     1560
ACACCCCATY TACCTGAGTC TGATTCTTTA GCAGCAGAGA CTGAGGGGTG CAGAGTGTGA     1620
GCTGGGAAAG GTTTGTGGCT CCTTGCAGCC TCCAGGGA CTGCTGTCCC CGATAGAATT     1680
GAAGCAGTCC ACGGGGAGGG GATGATACAA GGAGTAAACC TTTCTTTACA CTCTGAGGTC     1740
TCCAAAACAT TTGTTGTTAT C                                             1761

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## (2) INFORMATION FOR SEQ ID NO:2:

- (1) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 351 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Met Val Ile Met Gly Gln Cys Tyr Tyr Asn Glu Thr Ile Gly Phe Phe
 1           5           10           15

Tyr Asn Asn Ser Gly Lys Glu Leu Ser Ser His Trp Arg Pro Lys Asp
 20           25           30

Val Val Val Val Ala Leu Gly Leu Thr Val Ser Val Leu Val Leu Leu
 35           40           45

Thr Asn Leu Leu Val Ile Ala Ala Ile Ala Ser Asn Arg Arg Phe His
 50           55           60

Gln Pro Ile Tyr Tyr Leu Leu Gly Asn Leu Ala Ala Ala Asp Leu Phe
 65           70           75           80

Ala Gly Val Ala Tyr Leu Phe Leu Met Phe His Thr Gly Pro Arg Thr
 85           90           95

Ala Arg Leu Ser Leu Glu Gly Trp Phe Leu Arg Gln Gly Leu Leu Asp
 100          105          110

Thr Ser Leu Thr Ala Ser Val Ala Thr Leu Leu Ala Ile Ala Val Glu
 115          120          125

Arg His Arg Ser Val Met Ala Val Gln Leu His Ser Arg Leu Pro Arg
 130          135          140

Gly Arg Val Val Met Leu Ile Val Gly Val Trp Val Ala Ala Leu Gly
 145          150          155          160

Leu Gly Leu Leu Pro Ala His Ser Trp His Cys Leu Cys Ala Leu Asp
 165          170          175

Arg Cys Ser Arg Met Ala Pro Leu Leu Ser Arg Ser Tyr Leu Ala Val
 180          185          190

Trp Ala Leu Ser Ser Leu Leu Val Phe Leu Leu Met Val Ala Val Tyr
 195          200          205

Thr Arg Ile Phe Leu Tyr Val Arg Arg Arg Val Gln Arg Met Ala Glu
 210          215          220

His Val Ser Cys His Pro Arg Tyr Arg Glu Thr Thr Leu Ser Leu Val
 225          230          235          240

Lys Thr Val Val Ile Ile Leu Gly Ala Phe Val Val Cys Trp Thr Pro
 245          250          255

Gly Gln Val Val Leu Leu Leu Asp Gly Leu Gly Cys Glu Ser Cys Asn
 260          265          270

Val Leu Ala Val Glu Lys Tyr Phe Leu Leu Leu Ala Glu Ala Asn Ser
 275          280          285

Leu Val Asn Ala Ala Val Tyr Ser Cys Arg Asp Ala Glu Met Arg Arg
 290          295          300

Thr Phe Arg Arg Leu Leu Cys Cys Ala Cys Leu Arg Gln Pro Thr Arg
 305          310          315          320

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Glu Ser Val His Tyr Thr Ser Ser Ala Gln Gly Gly Ala Ser Thr Arg  
 325 330 335  
 Ile Met Leu Pro Glu Asn Gly His Pro Leu Met Asp Ser Thr Leu  
 340 345 350

## (2) INFORMATION FOR SEQ ID NO:3:

## (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1889 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: cDNA

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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TTACGAATTA ATACGATCAC TATAGGGAGA CCAAGCTTGG TACCGAGCTC GGATCCACTA      60
GTAACGGCCG CCAAGTGTGGG GAATTCGCT CCCGCCGAG TCGCCGGGCC ATGGGCCTCG      120
AGCCCGCCCC GAACCCCGC GAGCCCGCCT TGTCTGCGGC GTGACTGGAG GCCCAGATGG      180
TCATCATGGG CCAAGTGTAC TACAACGAGA CCATCGGTTT CTTCTATAAC AACAGTGGCA      240
AAGAGCTCAG CTCCCACTGG CGGCCCAAGG ATGTGGTCGT GGTGGCACTG GGGCTGACCG      300
TCAGCGTGCT GGTGCTGTG ACCAATCTGC TGGTCATAGC AGCCATCGCC TCCAACCGCC      360
GCTTCCACCA GCCCATCTAC TACCTGCTCG GCAATCTGGC CGCGGCTGAC CTCTTCGCGG      420
GCGTGGCCTA CCTCTTCCTC ATGTTCCACA CTGGTCCCCG CACAGCCCGA CTTTCACTTG      480
AGGGCTGGTT CCTGCGGCAG GGCTTGCTGG ACACAAGCCT CACTGCGTCG GTGGCCACAC      540
TGCTGGCCAT CGCCGTGGAA CGGCACCGCA GTGTGATGGC CGTACAGTTG CACAGCCGCC      600
TGCCCCGTGG CCGCGTGGTC ATGCTCATTG TGGGCGTGTG GGTGGCTGCC CTGGGCCTGG      660
GGCTGTGGCC TGCCCACTCC TGGCACTGCC TCTGTGCCCT GGACCGCTGC TCACGCATGG      720
CACCCCTGCT CAGCCGCTCC TATTTGGCCG TCTGGGCTCT GTCGAGCCTG CTTGTCTTCC      780
TGCTCATGGT GGCTGTGTAC ACCCGCATTT TTTTATACGT GCGGCGGCGA GTGCAGCGCA      840
TGGCAGAGCA TGTCACTGC CACCCCGCT ACCGAGAGAC CACGCTCAGC CTGGTCAAGA      900
CTGTTGTCAT CATCCTGGGG GCGTTCGTGG TCTGCTGGAC ACCAGGCCAG GTGGTACTGC      960
TCCTGGATGG TTTAGGCTGT GAGTCCTGCA ATGTCCTGGC TGTAGAAAAG TACTTCCTAC     1020
TGTTGGCCGA GGCCAACTCA CTGGTCAATG CTGCTGTGTA CTCTTGCCGA GATGCTGAGA     1080
TGCGCCGCAC CTTCCGCCGC CTTCTCTGCT GCGCGTGCCT CCGCCAGCCC ACCCGCGAGT     1140
CTGTCCACTA TACATCTCTT GCCCAGGGAG GTGCCAGCAC TGCATCATG CTTCCCGAGA     1200
ACGGCCACCC ACTGATGGAC TCCACCCTTT AGTACCTTG AACTTCAGCG GTACGCGGCA      1260
AGCAACAAAT CCACAGCCCC TGATGACTTG TGGGTGCTCC TGGCTCAACC CAACCAACAG      1320

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GACTGACTGA CCGGCAGGAC AAGGTCTGGC ATGGCACAGC ACCACTGCCA GGCCTCCCCA 1380
GGCACACCAC TCTGCCCAGG GAATGGGGGC TTTGGGTCAT CTCCCACTGC CTGGGGGAGT 1440
CAGATGGGGT GCAGGAATCT GGCTCTTCAG CCATCCCAGG TTTAGGGGGT TTGTAACAGA 1500
CATTATTCTG TTTTCACTGC GTATCCTTGG TAAGCCCTGT GGACTGGTTC CTGCTGTGTG 1560
ATGCTGAGGG TTTTAAGGTG GGGAGAGATA AGGGCTCTCT CGGGCCATGC TACCCGGTAT 1620
GACTGGGTAA TGAGGACAGA CTGTGGACAC CCCATYTACC TGAGTCTGAT TCTTTAGCAG 1680
CAGAGACTGA GGGGTGCAGA GTGTGAGCTG GGAAAGGTTT GTGGCTCCTT GCAGCCTCCA 1740
GGGACTGGCC TGTCCCCGAT AGAATTGAAG CAGTCCACGG GGAGGGGATG ATACAAGGAG 1800
TAAACCTTTC TTTCACTCT GAGGTCTCCA AAACATTTGT TGTTATCAA AAAAAAAAAA 1860
AAAAAAAAA AAAAAAAAAA AGCGGCCGC 1889

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## (2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 26 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGTGGTACTG CTCCTGGATG GTTTAG

26

## (2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 24 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CGGAGGCACG CGCAGCAGAG AAGA

24

## (2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 19 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TAGAGAACCC ACTGCTTAC

19

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 19 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCCAGAATAG AATGACACC

19

**THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE  
PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:**

1. An isolated nucleic acid molecule wherein said nucleic acid molecule encodes a polypeptide having an amino acid sequence as shown in SEQ. ID NO:2.
2. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid is DNA.
3. The isolated nucleic acid of claim 2 wherein said nucleic acid is selected from the group consisting of:
  - a) the nucleotide sequence as shown in SEQ. ID NO:1;
  - b) nucleotide sequences that hybridize to SEQ. ID NO:1 or to its complementary strand;
  - c) nucleotide sequences that differ from SEQ. ID NO:1 and from the nucleotide sequences of (b) in codon sequence due the degeneracy of the genetic code.
4. The isolated nucleic acid of claim 2 wherein said nucleic acid includes the nucleotide sequence as shown in SEQ. ID NO:1.
5. The isolated nucleic acid of claim 1 wherein said nucleic acid is RNA.
6. An isolated nucleic acid which is anti-sense to a nucleic acid as claimed in claim 1.
7. An isolated nucleic acid which is anti-sense to a nucleic acid as claimed in claim 3.
8. An isolated nucleic acid which is anti-sense to a nucleic acid as claimed in claim 4
9. The isolated nucleic acid of claim 1 which is an RNA anti-sense sequence.
10. A DNA construct comprising the following operably linked elements:
  - a) a transcriptional promoter;
  - b) a DNA sequence including the nucleotide sequence as shown in SEQ. ID NO:1;and,
  - c) a transcriptional terminator.
11. The DNA construct of claim 10 wherein said DNA sequence encodes the polypeptide of SEQ. ID NO:2.
12. A recombinant expression vector suitable for transformation of a host cell comprising a nucleic acid as claimed in claim 1 and a regulatory sequence operatively linked to said nucleic acid.
13. A recombinant expression vector suitable for transformation of a host cell comprising a DNA molecule having a nucleotide sequence as shown in SEQ. ID NO:1 and a regulatory sequence operatively linked to said DNA molecule.

14. The recombinant expression vector of claim 13 wherein the DNA molecule is operatively linked to the regulatory sequence to allow expression of an RNA molecule which is anti-sense to a nucleotide sequence as shown in SEQ. ID NO:1.
15. A transformed cell including a recombinant expression vector as claimed in claim 12.
- 5 16. A transformed cell including a recombinant expression vector as claimed in claim 13.
17. A method for preparing an isolated protein having an amino acid sequence as shown in SEQ. ID NO:2 said method comprising culturing a transformed cell including a recombinant expression vector as claimed in claim 13 in a suitable medium until the protein is formed and isolating said protein.
- 10 18. The polypeptide expressed by the expression vector of claim 13.
19. pharmaceutical composition comprising the antisense molecule of claim 3 and a pharmaceutically acceptable carrier.
20. A probe comprising an oligonucleotide of the nucleic acid as shown in SEQ. ID NO:1 capable of specifically hybridizing with a gene which encodes a protein having an amino acid
- 15 sequence as shown in SEQ. ID NO:2 or allelic and species variants thereof.
21. An isolated polypeptide having the amino acid sequence as shown in SEQ. ID NO:2.
22. A purified polyclonal antibody specific for the amino acid sequence as shown in SEQ. ID NO:2.
23. The purified polyclonal antibody of claim 22 wherein said antibody is specific for an
- 20 extracellular epitope of the protein having the amino acid sequence as shown in SEQ. ID NO:2.
24. The purified polyclonal antibody of claim 22 wherein the antibody is labeled.
25. A monoclonal antibody specific for the amino acid sequence as shown in SEQ. ID NO:2.
- 25 26. The monoclonal antibody of claim 25 wherein said antibody is specific for an extracellular epitope of the protein having the amino acid sequence as shown in SEQ. ID NO:2.
27. The monoclonal antibody of claim 25 wherein the antibody is labeled.
28. The method for determining the presence of a protein having an amino acid sequence
- 30 as shown in SEQ. ID NO:2 in a biological sample, the method comprising the steps of:
- a) incubating the sample with a monoclonal antibody or purified polyclonal antibody which specifically binds to an epitope of said protein under conditions sufficient for the formation of an immune complex; and,

- b) determining the presence of said immune complex.
29. The method of claim 28 wherein the monoclonal or purified polyclonal antibody is labeled.
30. A method of purifying a protein having the amino acid sequence as shown in SEQ. ID NO:2, the method including an immunoaffinity chromatography process wherein a monoclonal antibody or a purified polyclonal antibody specific to an epitope of said protein is immobilized on the chromatography resin.
31. A method of screening a molecule which ligates to the protein having the amino acid sequence as shown in SEQ. ID NO:2 comprising a signal transduction assay.
- 10 32. The method of claim 31, wherein the protein is a G protein coupled receptor, the method comprising the following steps:
- a) co-transfecting into a suitable cell of a plasmid including a reporter gene and an expression plasmid coding for said protein;
  - b) expressing said protein;
  - 15 c) treating said cell with serum starvation to reduce mitogenic activity;
  - d) applying said molecule which ligates to said protein in a serum free medium; and,
  - e) measuring the activity of the reporter.
33. A transgenic animal expressing a first transgene coding for a protein having an amino acid sequence as shown in SEQ. ID NO:2.
- 20 34. The transgenic animal of claim 33 wherein said first transgene comprises a polynucleotide having a nucleotide sequence as shown in SEQ. ID NO:1.
35. A transgenic animal as claimed in claim 33 further including a second transgene coding for an inducible promoter for said first transgene.
36. A transgenic animal as claimed in claim 33 further including a second transgene coding for a tissue specific regulatory element for regulating the expression of said first transgene.
- 25

## AMENDED CLAIMS

[received by the International Bureau on 6 November 1998 (06.11.98);  
original claims 1-36 replaced by amended claims 1-22 (3 pages)].

- 5 1. An isolated nucleic acid molecule wherein the molecule is selected from the group consisting of :
- a) a molecule having a nucleic acid sequence as shown in SEQ. ID. NO: 1; and
  - b) hybridizing nucleic acid molecules that hybridize to a molecule having a nucleic acid sequence as shown in SEQ. ID NO:1 or to complementary strands thereof, said
- 10 hybridizing nucleic acid molecules having at least 40% homology with a molecule having a nucleic acid sequence as shown in SEQ. ID NO:1.
2. The molecule of claim 1 wherein said hybridizing nucleic acid molecule hybridizes to SEQ. ID NO:1 under stringent conditions.
- 15 3. The molecule of claim 1 wherein said hybridizing nucleic acid molecule has at least 85% homology with a molecule having a nucleic acid sequence as shown in SEQ. ID NO:1.
4. The molecule of claim 1 wherein said hybridizing nucleic acid molecule has at least
- 20 90% homology with a molecule having a nucleic acid sequence as shown in SEQ. ID NO:1.
5. The molecule of claim 1 wherein said hybridizing nucleic acid molecule has at least 95% sequence identity with a molecule having a nucleic acid sequence as shown in SEQ. ID NO:1.
- 25 6. A DNA construct comprising the following operably linked elements:
- a) a transcriptional promoter;
  - b) a DNA sequence including the nucleotide sequence as claimed in claim 2; and,
  - c) a transcriptional terminator.
- 30 7. A recombinant expression vector suitable for transformation of a host cell comprising a nucleic acid as claimed in claim 2 and a regulatory sequence operatively linked to said nucleic acid.

8. A transformed cell including a recombinant expression vector as claimed in claim 7.
9. A method for preparing an isolated amino acid sequence as claimed in claim 2, said method comprising culturing a transformed cell as claimed in claim 8 in a suitable medium  
5 until the protein is formed and isolating said protein.
10. The polypeptide expressed by the recombinant expression vector of claim 7.
11. A probe comprising an oligonucleotide of the nucleic acid as claimed in claim 2  
10 capable of specifically hybridizing with a gene which encodes a protein having an amino acid sequence as shown in SEQ. ID. NO: 2 or allelic and species variants thereof.
12. A purified polyclonal antibody specific for the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.  
15
13. The purified polyclonal antibody of claim 12 wherein the antibody is specific for an extracellular epitope of the protein having the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.
- 20 14. The purified polyclonal antibody of claim 12 wherein the antibody is labeled.
15. A monoclonal antibody specific for the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.
- 25 16. The monoclonal antibody of claim 15 wherein said antibody is specific for an extracellular epitope of the protein having the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.
17. The monoclonal antibody of claim 15 wherein the antibody is labeled.  
30

8. A transformed cell including a recombinant expression vector as claimed in claim 7.
9. A method for preparing an isolated amino acid sequence as claimed in claim 2, said method comprising culturing a transformed cell as claimed in claim 8 in a suitable medium  
5 until the protein is formed and isolating said protein.
10. The polypeptide expressed by the recombinant expression vector of claim 7.
11. A probe comprising an oligonucleotide of the nucleic acid as claimed in claim 2  
10 capable of specifically hybridizing with a gene which encodes a protein having an amino acid sequence as shown in SEQ. ID. NO: 2 or allelic and species variants thereof.
12. A purified polyclonal antibody specific for the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.  
15
13. The purified polyclonal antibody of claim 12 wherein the antibody is specific for an extracellular epitope of the protein having the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.
- 20 14. The purified polyclonal antibody of claim 12 wherein the antibody is labeled.
15. A monoclonal antibody specific for the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.
- 25 16. The monoclonal antibody of claim 15 wherein said antibody is specific for an extracellular epitope of the protein having the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof.
17. The monoclonal antibody of claim 15 wherein the antibody is labeled.  
30

18. The method for determining the presence of a protein having an amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof in a biological sample, the method comprising the steps of:

- a) incubating the sample with amonoclonal antibody or purified polyclonal antibody which specifically binds to an epitope of said protein under conditions sufficient for the formation of an immune complex; and,
- b) determining the presence of said immune complex.

19. The method of claim 18 wherein the monoclonal or purified polyclonal antibody is labeled.

20. A method of purifying a protein having the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants thereof, the method including an immunoaffinity chromatography process wherein a monoclonal antibody or a purified polyclonal antibody specific to an epitope of said protein is immobilized on the chromatography resin.

21. A method of screening a molecule which ligates to the protein having the amino acid sequence as shown in SEQ. ID. NO: 2 or allelic variants or fragments thereof comprising a signal transduction assay.

20

22. The method of claim 21, wherein the protein is a G protein coupled receptor, the method comprising the following steps:

- a) co-transfecting into a suitable cell of a plasmid including a reporter gene and an expression plasmid coding for said protein;
- b) expressing said protein;
- c) treating said cell with serum starvation to reduce mitogenic activity;
- d) applying said molecule which ligates to said protein in a serum free medium; and
- e) measuring the activity of the reporter.

30

**Figure 1**

**hedg-6 cDNA and predicted amino acid sequence. The cloning sites and poly(A) tail have been excluded from this figure.**

**Figure 1A**

SEQ. ID NO:1

```
CGCTCCCGCCGCGAGTCGCCGGGCCATGGGCCTCGAGCCCGCCCCGAACCCCGCGAGCCC
GCGAGGGCGGGCGTCAGCGGCCCGGTACCCGGAGCTCGGGCGGGGCTTGGGGCGCTCGGG
1  -----+-----+-----+-----+-----+-----+ 60
```

**Figure 1B**

SEQ. ID NO:2

```
                M V I M G Q C Y Y N
GCCTTGTCTGCGGCGTGACTGGAGGCCAGATGGTCATCATGGGCCAGTGCTACTACAAC
CGGAACAGACGCCGCACTGACCTCCGGGTCTACCAGTAGTACCCGGTCACGATGATGTTG
61  -----+-----+-----+-----+-----+-----+ 120

E T I G F F Y N N S G K E L S S H W R P
GAGACCATCGGTTTCTTCTATAACAACAGTGGCAAAGAGCTCAGTCCCACTGGCGGGCC
CTCTGGTAGCCAAAGAAGATATTGTTGTCACCGTTTCTCGAGTCGAGGGTGACCGCCGGG
121 -----+-----+-----+-----+-----+-----+ 180

K D V V V V A L G L T V S V L V L L T N
AAGGATGTGGTTCGTGGTGGCACTGGGGCTGACCGTCAGCGTGCTGGTGCTGCTGACCAAT
TTCTACACCAGCACCACCGTGACCCGACTGGCAGTCGCACGACCACGACGACTGGTTA
181 -----+-----+-----+-----+-----+-----+ 240

L L V I A A I A S N R R F H Q P I Y Y L
CTGCTGGTCATAGCAGCCATCGCCTCCAACCGCCGCTTCCACCAGCCCATCTACTACCTG
GACGACCAGTATCGTTCGGTAGCGGAGGTTGGCGGCGAAGGTGGTCGGGTAGATGATGGAC
241 -----+-----+-----+-----+-----+-----+ 300

L G N L A A A D L F A G V A Y L F L M F
CTCGGCAATCTGGCCGCGGCTGACCTCTTCGGGGCGTGGCTACCTCTTCTCATGTTC
GAGCCGTTAGACCGGCGCCGACTGGAGAAGCGCCGACCGGATGGAGAAGGAGTACAAG
```

301 -----+-----+-----+-----+-----+-----+ 360

H T G P R T A R L S L E G W F L R Q G L  
CACACTGGTCCCCGCACAGCCGACTTTCACTTGAGGGCTGGTTCCTGCGGCAGGGCTTG  
GTGTGACCAGGGGCGTGTCTGGGCTGAAAGTGAAGTCCCGACCAAGGACGCCGTCCCGAAC

361 -----+-----+-----+-----+-----+-----+ 420

L D T S L T A S V A T L L A I A V E R H  
CTGGACACAAGCCTCACTGCGTCGGTGGCCACACTGCTGGCCATCGCCGTGGAACGGCAC  
GACCTGTGTTCTGGAGTGACGCAGCCACCGGTGTGACGACCGGTAGCGGCACCTTGCCGTG

421 -----+-----+-----+-----+-----+-----+ 480

R S V M A V Q L H S R L P R G R V V M L  
CGCAGTGTGATGGCCGTACAGTTGCACAGCCGCTGCCCCGTGGCCGCGTGGTCATGCTC  
GCGTCACACTACCGGCATGTCAACGTGTCTGGCGGACGGGGACCGGCGCACAGTACGAG

481 -----+-----+-----+-----+-----+-----+ 540

I V G V W V A A L G L G L L P A H S W H  
ATTGTGGGCGTGTGGGTGGCTGCCCTGGGCTGGGGCTGTTGCCTGCCCCACTCCTGGCAC  
TAACACCCGCACACCCACCGACGGGACCCGGACCCCGACAACGGACGGGTGAGGACCGTG

541 -----+-----+-----+-----+-----+-----+ 600

C L C A L D R C S R M A P L L S R S Y L  
TGCCTCTGTGCCCTGGACCGCTGCTCACGCATGGCACCCCTGCTCAGCCGCTCCTATTTG  
ACGGAGACACGGGACCTGGCGACGAGTGCGTACCGTGGGGACGAGTCGGCGAGGATAAAC

601 -----+-----+-----+-----+-----+-----+ 660

A V W A L S S L L V F L L M V A V Y T R  
GCCGCTCTGGGCTCTGTGAGCCTGCTTGTCTTCCTGCTCATGGTGGCTGTGTACACCCGC  
CGGCAGACCCGAGACAGCTCGGACGAACAGAAGGACGAGTACCACCGACACATGTGGGCG

661 -----+-----+-----+-----+-----+-----+ 720

I F L Y V R R R V Q R M A E H V S C H P  
ATTTTTTTATACGTGCGGCGGCGAGTGCAGCGCATGGCAGAGCATGTCAGCTGCCACCCC  
TAAAAAATATGCACGCCGCCGCTCACGTGCGGTACCGTCTCGTACAGTCGACGGTGGGG  
721 -----+-----+-----+-----+-----+-----+ 780  
R Y R E T T L S L V K T V V I I L G A F  
CGCTACCGAGAGACCACGCTCAGCCTGGTCAAGACTGTTGTCATCATCCTGGGGGCGTTC  
GCGATGGCTCTCTGGTGCGAGTCGGACCAGTTCTGACAACAGTAGTAGGACCCCGCAAG  
781 -----+-----+-----+-----+-----+-----+ 840  
  
V V C W T P G Q V V L L L D G L G C E S  
GTGGTCTGCTGGACACCAGGCCAGGTGGTACTGCTCCTGGATGGTTAGGCTGTGAGTCC  
CACCAGACGACCTGTGGTCCGGTCCACCATGACGAGGACCTACCAAATCCGACACTCAGG  
841 -----+-----+-----+-----+-----+-----+ 900  
  
C N V L A V E K Y F L L L A E A N S L V  
TGCAATGTCCTGGCTGTAGAAAAGTACTTCTACTGTTGGCCGAGGCCAACTACTGGTC  
ACGTTACAGGACCGACATCTTTTCATGAAGGATGACAACCGGCTCCGGTTGAGTGACCAG  
901 -----+-----+-----+-----+-----+-----+ 960  
  
N A A V Y S C R D A E M R R T F R R L L  
AATGCTGCTGTGTACTCTTGCCGAGATGCTGAGATGCGCCGACCTTCCGCCGCTTCTC  
TTACGACGACACATGAGAACGGCTCTACGACTCTACGCGGCGTGAAGGCGGCGGAAGAG  
961 -----+-----+-----+-----+-----+-----+  
1020  
  
C C A C L R Q P T R E S V H Y T S S A Q  
TGCTGCGCGTGCCTCCGCCAGCCACCCGCGAGTCTGTCCACTATACATCCTCTGCCAG  
ACGACGCGCACGGAGGCGGTGCGGTGGGCGCTCAGACAGGTGATATGTAGGAGACGGGTC  
1021 -----+-----+-----+-----+-----+-----+  
1080  
  
G G A S T R I M L P E N G H P L M D S T  
GGAGGTGCCAGCACTCGCATCATGCTTCCCGAGAACGGCCACCCACTGATGGACTCCACC

CCTCCACGGTCGTGAGCGTAGTACGAAGGGCTCTTGCCGGTGGGTGACTACCTGAGGTGG  
1081 -----+-----+-----+-----+-----+-----+  
1140

L \*  
CTTTAGCTACCTTGAACCTCAGCGGTACGCGGCAAGCAACAAATCCACAGCCCCTGATGA  
GAAATCGATGGAACCTGAAGTCGCCATGCGCCGTTTCGTTGTTTAGGTGTCGGGGACTACT  
1141 -----+-----+-----+-----+-----+-----+  
1200

CTTGTGGGTGCTCCTGGCTCAACCCAACCAACAGGACTGACTGACCGGCAGGACAAGGTC  
GAACACCCACGAGGACCGAGTTGGGTTGGTTGTCCTGACTGACTGGCCGTCCTGTTCCAG  
1201 -----+-----+-----+-----+-----+-----+  
1260

TGGCATGGCACAGCACCCTGCCAGGCCCTCCCAGGCACACCACTCTGCCCAGGGAATGG  
ACCGTACCGTGTCGTGGTGACGGTCCGGAGGGGTCCGTGTGGTGAGACGGGTCCCTTACC  
1261 -----+-----+-----+-----+-----+-----+  
1320

GGGCTTTGGGTCATCTCCCACTGCCTGGGGGAGTCAGATGGGGTGACGGAATCTGGCTCT  
CCCGAAACCCAGTAGAGGGTGACGGACCCCTCAGTCTACCCACGTCCTTAGACCGAGA  
1321 -----+-----+-----+-----+-----+-----+  
1380

TCAGCCATCCCAGGTTTAGGGGTTTGTAACAGACATTATTCTGTTTTCACTGCGTATCC  
AGTCGGTAGGGTCCAAATCCCCCAAACATTGTCTGTAATAAGACAAAAGTGACGCATAGG  
1381 -----+-----+-----+-----+-----+-----+  
1440

TTGGTAAGCCCTGTGGACTGGTTCCCTGCTGTGTGATGCTGAGGGTTTTAAGGTGGGGAGA  
AACCATTTCGGGACACCTGACCAAGGACGACACACTACGACTCCCAAATTCACCCCTCT

1441 -----+-----+-----+-----+-----+-----+  
1500  
  
GATAAGGGCTCTCTCGGGCCATGCTACCCGGTATGACTGGGTAATGAGGACAGACTGTGG  
CTATTCGAGAGAGAGCCCGGTACGATGGGCCATACTGACCCATTACTCCTGTCTGACACC  
1501 -----+-----+-----+-----+-----+-----+  
1560  
  
ACACCCCATYTACCTGAGTCTGATTCTTTAGCAGCAGAGACTGAGGGGTGCAGAGTGTGA  
TGTGGGGTARATGGACTCAGACTAAGAAATCGTCGTCTCTGACTCCCCACGTCTCACACT  
1561 -----+-----+-----+-----+-----+-----+  
1620  
  
GCTGGGAAAGGTTTGTGGCTCCTTGACGCCTCCAGGGACTGGCCTGTCCCCGATAGAATT  
CGACCCCTTTCCAAACACCGAGGAACGTCGGAGGTCCCTGACCGGACAGGGGCTATCTTAA  
1621 -----+-----+-----+-----+-----+-----+  
1680  
  
GAAGCAGTCCACGGGGAGGGGATGATACAAGGAGTAAACCTTTCTTTACACTCTGAGGTC  
CTTCGTCAGGTGCCCCCTCCCCTACTATGTTCTCATTGGGAAAGAAATGTGAGACTCCAG  
1681 -----+-----+-----+-----+-----+-----+  
1740  
  
TCCAAAACATTTGTTGTTATC  
AGGTTTTGTAAACAACAATAG  
1741 -----+-----+-----+-----+-----+-----+ 1761

**Figure 2**

**Nucleotide sequence of human edg-6 cDNA insert. Sequence includes the EcoRI (position 81) and NotI (position 1882) cloning sites and the 34 bp poly(A) tail**

SEQ. ID NO:3

```

1  TTACGAATTAATACGATCACTATAGGGAGACCAAGCTTGGTACCGAGCTCGGATCCAATA
   -----+-----+-----+-----+-----+-----+
61  GTAACGGCCGCCAGTGTGGGAATTCCGCTCCCGCCGAGTCGCCGGGCCATGGGCCTCG
   -----+-----+-----+-----+-----+-----+
121 AGCCCGCCCCGAACCCCGGAGCCCGCCTTGTCTGCGGCGTACTGGAGGCCAGATGG
   -----+-----+-----+-----+-----+-----+
181 TCATCATGGGCCAGTGCTACTACAACGAGACCATCGGTTTCTTATAACAACAGTGGCA
   -----+-----+-----+-----+-----+-----+
241 AAGAGCTCAGTCCCACTGGCGGCCAAGGATGTGGTCGTGGTGGCACTGGGGCTGACCG
   -----+-----+-----+-----+-----+-----+
301 TCAGCGTGTGGTGTCTGCTGACCAATCTGCTGGTCATAGCAGCCATCGCCTCCAACCGCC
   -----+-----+-----+-----+-----+-----+
361 GCTTCCACCAGCCCATCTACTACCTGCTCGGCAATCTGGCCGCGGCTGACCTCTTCGCGG
   -----+-----+-----+-----+-----+-----+
421 GCGTGGCCTACCTCTTCCTCATGTTCCACACTGGTCCCGCACAGCCGACTTTCCTTG
   -----+-----+-----+-----+-----+-----+
481 AGGGCTGGTTCCTGCGGCAGGGCTTGCTGGACACAAGCCTCACTGCGTCGGTGGCCACAC
   -----+-----+-----+-----+-----+-----+
541 TGCTGGCCATCGCCGTGGAACGGCACCAGTGTGATGGCCGTACAGTTGCACAGCCGCC
   -----+-----+-----+-----+-----+-----+
601 TGCCCCGTGGCCGCGTGGTCACTGCTCATTGTGGGCGTGTGGGTGGCTGCCCTGGGCCTGG
   -----+-----+-----+-----+-----+-----+
661 GGCTGTTGCCTGCCCACTCCTGGCACTGCCTCTGTGCCCTGGACCGCTGCTCAGCATGG
   -----+-----+-----+-----+-----+-----+
721 CACCCCTGCTCAGCCGCTCCTATTTGGCCGTCTGGGCTCTGTCGAGCCTGCTTGTCTTCC
   -----+-----+-----+-----+-----+-----+
781 TGCTCATGGTGGCTGTGTACACCCGATTTTTTATACGTGCGGCGGAGTGCAGCGCA
   -----+-----+-----+-----+-----+-----+
841 TGGCAGAGCATGTCAGTGCACCCCGCTACCGAGAGACCACGCTCAGCCTGGTCAAGA
   -----+-----+-----+-----+-----+-----+
901 CTGTTGTCATCATCCTGGGGCGTTCGTGGTCTGCTGGACACCAGGCCAGGTGGTACTGC
   -----+-----+-----+-----+-----+-----+
961 TCCTGGATGGTTTAGGCTGTGAGTCTGCAATGTCCTGGCTGTAGAAAAGTACTTCCTAC
   -----+-----+-----+-----+-----+-----+
1021 TGTTGGCCGAGGCCAACTCACTGGTCAATGCTGCTGTGTACTCTTGCCGAGATGCTGAGA
   -----+-----+-----+-----+-----+-----+
1081 TGCGCCGACCTTCCGCCGCTTCTCTGCTGCGCGTGCCTCCGCCAGCCACCCGCGAGT
   -----+-----+-----+-----+-----+-----+
1140

```

CTGTCCACTATACATCCTCTGCCCAGGGAGGTGCCAGCACTCGCATCATGCTTCCCGAGA  
1141 -----+-----+-----+-----+-----+-----+-----+ 1200  
ACGGCCACCCACTGATGGACTCCACCCTTTAGCTACCTTGAACCTCAGCGGTACGCGGCA  
1201 -----+-----+-----+-----+-----+-----+-----+ 1260  
AGCAACAAATCCACAGCCCCCTGATGACTTGTGGGTGCTCCTGGCTCAACCCAACCAACAG  
1261 -----+-----+-----+-----+-----+-----+-----+ 1320  
GACTGACTGACCGGCAGGACAAGGTCTGGCATGGCAGCACCCTGCCAGGCCTCCCCA  
1321 -----+-----+-----+-----+-----+-----+-----+ 1380  
GGCACACCACTCTGCCCAGGGAATGGGGCTTTGGGTCTCTCCCACTGCCTGGGGGAGT  
1381 -----+-----+-----+-----+-----+-----+-----+ 1440  
CAGATGGGTGCAGGAATCTGGCTCTTCAGCCATCCCAGGTTTAGGGGGTTGTAAACAGA  
1441 -----+-----+-----+-----+-----+-----+-----+ 1500  
CATTATTCTGTTTTCACTGCGTATCCTTGTAAGCCCTGTGGACTGGTTCCTGCTGTGTG  
1501 -----+-----+-----+-----+-----+-----+-----+ 1560  
ATGCTGAGGGTTTTAAGGTGGGGAGAGATAAGGGCTCTCTCGGGCCATGCTACCCGGTAT  
1561 -----+-----+-----+-----+-----+-----+-----+ 1620  
GACTGGGTAATGAGGACAGACTGTGGACACCCATYTACCTGAGTCTGATTCTTTAGCAG  
1621 -----+-----+-----+-----+-----+-----+-----+ 1680  
CAGAGACTGAGGGGTGCAGAGTGTGAGCTGGGAAAGGTTTGTGGCTCCTTGACGCTCCA  
1681 -----+-----+-----+-----+-----+-----+-----+ 1740  
GGGACTGGCCTGTCCCCGATAGAATTGAAGCAGTCCACGGGGAGGGGATGATACAAGGAG  
1741 -----+-----+-----+-----+-----+-----+-----+ 1800  
TAAACCTTTCTTTACACTCTGAGGTCTCCAAAACATTGTGTATCAAAAAAAAAAAAAA  
1801 -----+-----+-----+-----+-----+-----+-----+ 1860  
AAAAAAAAAAAAAAAAAAAAAGCGCCGC  
1861 -----+-----+-----+-----+-----+-----+-----+ 1889

# INTERNATIONAL SEARCH REPORT

Intern. nal Application No

PCT/CA 98/00487

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/705 C12N5/10 C07K16/28 G01N33/563  
G01N33/50 A61K31/70 A01K67/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N G01N A61K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 30406 A (CAO LIANG ; HUMAN GENOME SCIENCES INC (US); LI YI (US); NI JIAN (US) 3 October 1996	1-4, 6-8, 10-27, 31
Y	see the whole document	28-30
Y	WO 97 00952 A (INCYTE PHARMA INC) 9 January 1997	28-30
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	see the whole document	
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

15 October 1998

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA 98/00487

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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PCT/CA 98/00487

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